II. REMARKS

Formal Matters

Claims 1, 3, 5, 7, 14, 15, and 20-22 are pending after entry of the amendments set forth herein.

Claims 1, 3, 5, 7, 14, 15, and 20-23 were examined and were rejected.

Claim 1 is amended. The amendment to claim 1 was made solely in the interest of expediting prosecution, and is not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendment to claim 1 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraph 0038; and paragraph 0050. Accordingly, no new matter is added by this amendment.

Claim 23 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Advisory Action

The March 18, 2005 Advisory Action stated that the claim amendments made in the amendment, filed on February 25, 2005 and responsive to the October 1, 2004 final Office Action were entered. The March 18, 2005 Advisory Action stated that the Declaration of Karl Weisgraber, provided as Exhibit 1 along with the February 25, 2005 amendment, was not entered. Applicants respectfully request entry and consideration of the Declaration of Karl Weisgraber. A copy of the Declaration is provided herewith merely as a courtesy.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 3, 5, 7, 14, 15, and 20-23 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Advisory Action stated that the mouse as recited in claim 1 exhibits a phenotype of preferential binding to LDLs; and stated that the mouse fails to have a phenotype that would allow it to be used in the method of screening of claim 14. Applicants respectfully traverse the rejection.

As discussed in the amendment, filed on February 25, 2005 and responsive to the October 1, 2004 final Office Action, ApoE4 is known to be associated with various pathological conditions. The instant specification provides ample enablement for the use of a gene-targeted mouse as claimed, or a cell isolated therefrom.

The instant specification provides ample enablement for use of a gene-targeted mouse, or a cell isolated therefrom, as recited.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1), a cell isolated from such an animal, or a recombinant apoE polypeptide made by such an animal or a cell, is useful for carrying out drug screening assays to identifying agents that reduce apoE4 domain interaction. The specification provides a detailed description of how such drug screening assays would be performed.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with an apoE4-related neurological disorder. Specification, page 30, paragraph 00108; paragraph 00109; paragraph 0028; and paragraph 00196. The specification states that apoE-related neurological disorders include AD, poor outcome following a stroke, poor outcome following head injury, and cerebral ischemia. Specification, paragraph 0050. The specification states that apoE-related neurological disorders can be assessed by pathological studies, including an assessment of neurodegeneration. Specification, pages 39-40, paragraphs 00135-00136. The specification states that neuronal damage is assessed using well-known assays, including neuronal damage associated with traumatic brain injury and traumatic ischemic insult to the brain. Specification, pages 42-44, paragraphs 00145-00147.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with AD. Specification, page 8, paragraph 0029. The specification states that phenomena associated with AD include neuropathological developments. Specification, paragraph 0046. Such neuropathological developments include neurodegeneration. Specification, paragraph 00127; and paragraph 00128.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce cholesterol levels in an individual, and to treat hyperlipidemia in an individual Specification, page 8, paragraph 0030; page 44, paragraphs 00148-00150. The instant specification states that phenomena associated with apoE4-associated disorders

include high serum cholesterol levels. Specification, page 12, paragraph 0050.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce the risk of coronary artery disease and cardiovascular disorders. Specification, page 8, paragraph 0031; page 29, paragraph 00108; page 44, paragraphs 00148-00150; and paragraph 00196. The specification states that apoE-related disorders associated with high serum lipid levels include atherosclerosis and coronary artery disease. Specification, page 12, paragraph 0050. The specification states that the effect of a test agent on apoE4-related cardiovascular disorders can be assessed by pathological studies. Specification, page 40, paragraph 00137.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1), a cell isolated from such an animal, or a recombinant apoE polypeptide made by such an animal or a cell, is useful for identifying an agent that disrupts interaction of apoE with lower density lipoproteins. Specification, page 8, paragraph 0032; page 37-38, paragraphs 00131 and 00132.

The instant specification provides data showing that a gene-targeted mouse as claimed produces a modified apoE protein having Arg at a position equivalent to Arg-61 in human apoE4, and that the Arg-61 apoE produced by the gene-targeted mouse exhibits preferential binding to lower density lipoproteins. Specification, Example 1, e.g., paragraphs 00191, 00194, and 00195. These data demonstrate that the Arg-61 apoE protein produced by the gene-targeted mouse exhibits domain interaction, is a model for human apoE4 domain interaction, and is therefore useful for identifying agents that interfere with the domain interaction, which agents are useful to treat disorders such as cardiovascular diseases and neurodegenerative diseases associated with human apoE4. Specification, paragraph 00196.

In addition, a Declaration of Dr. Karl Weisgraber ("Weisgraber Declaration"), which was provided along with the amendment filed on February 25, 2005 as Exhibit 1, demonstrates that a gene-targeted mouse as claimed exhibits a degree of neurodegeneration that is greater than a control mouse. The data in the Weisgraber Declaration provide further support for the fact that a gene-targeted mouse as claimed is useful for identifying agents that treat apoE4-related neurodegeneration.

Thus, the instant specification enables use of a claimed gene-targeted mouse, and of a cell isolated from a claimed gene-targeted mouse, in screening for agents that treat a variety of disorders.

Accordingly, claims 1, 3, 5, 7, and 20-23 are in compliance with the enablement requirement of 35 U.S.C.§112, first paragraph.

The instant specification provides ample enablement for a method of identifying an agent that reduces a phenomenon associated with AD.

As discussed above, the instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with AD. Specification, page 8, paragraph 0029; and paragraph 00196. The specification states that phenomena associated with AD include neuropathological developments. Specification, paragraph 0046. Such neuropathological developments include neurodegeneration. Specification, paragraph 00127; and paragraph 00128.

Furthermore, as discussed above, the Weisgraber Declaration demonstrates that a gene-targeted mouse as claimed exhibits a degree of neurodegeneration that is greater than a control mouse. The data in the Weisgraber Declaration provide further support for the fact that a gene-targeted mouse as claimed is useful for identifying agents that treat apoE4-related neurodegeneration such as AD.

Thus, the instant specification enables use of a claimed gene-targeted mouse in a method of identifying agents that reduce a phenomenon associated with AD. Accordingly, claims 14 and 15 are in compliance with the enablement requirement of 35 U.S.C.§112, first paragraph.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to recite "wherein the mouse exhibits apoE4-related neurodegeneration."

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1, 3, 5, 7, 14, 15, and 20-23 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-222.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Mar. 31, 2005

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DECLARATION OF KARL WEISGRABER UNDER 37 C.F.R. § 1.132	Attorney Docket Confirmation No.	UCAL-222 5282
	First Named Inventor	Karl H. Weisgraber
	Application Number	10/017,718
	Filing Date	December 14, 2001
	Group Art Unit	1632
Address to: Commissioner for Patents Alexandria, VA 22313-1450	Examiner Name	T.N. Ton
	Title	*Gene-targeted animal model of apolipoprotein E4 domain interaction and uses thereof*

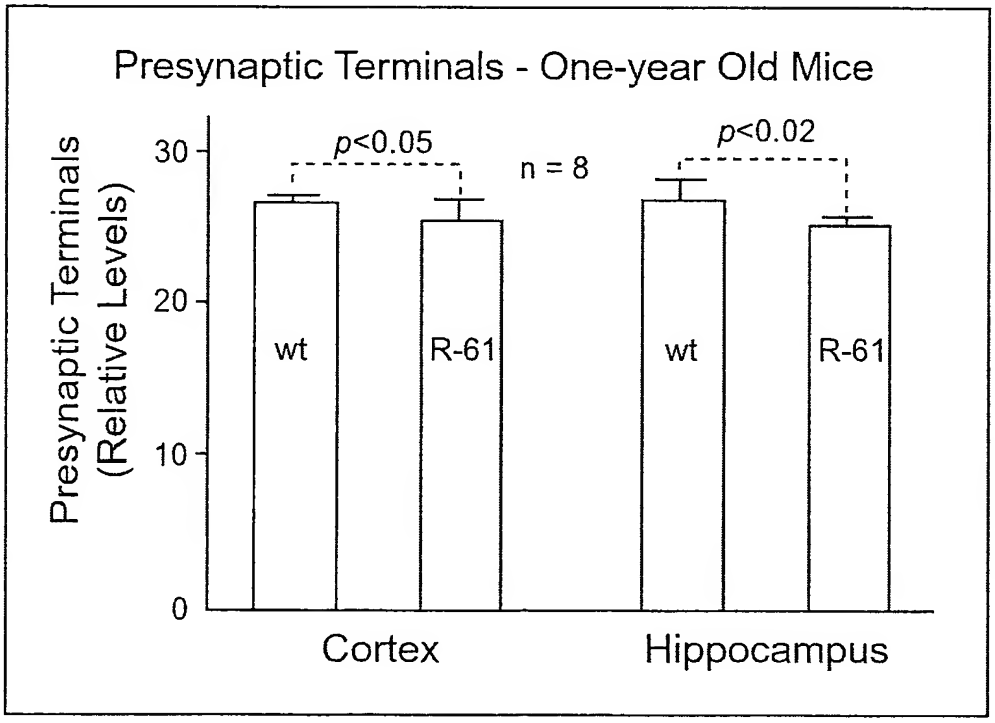
Dear Sir:

1. I, Karl Weisgraber, declare and say I am a co-inventor of the claims of the above-identified patent application.

2. I have read the Office Action dated October 1, 2004 in this application and understand that the Examiner would like to see further evidence that a gene-targeted mouse that produces an Arg-61 modified apoE exhibits a phenomenon associated with Alzheimer's Disease (AD).

3. The following paragraphs describe experiments conducted in my laboratory. The results of the experiments provide further evidence for the fact that a gene-targeted mouse that bears a Thr→Arg substitution at a position equivalent to Arg-61 in human apoE4 exhibits a phenomenon associated with AD, and therefore is suitable for use in identifying agents that reduce a phenomenon associated with AD.

4. Assessment of neurodegeneration in wild type (wt) and Arg-61 (R-61) mice by examination of presynaptic terminal density. Fixed hemi-brains from one-year mice were vibratome sectioned and the tissue sections were immunolabeled with a monoclonal antibody specific for synaptophysin (presynaptic terminals). The labeled sections were examined by confocal microscopy and computer-assisted analysis was used to quantitate the level of immunoreactive presynaptic terminals in the cortex and hippocampus, a validated method to measure neuronal integrity. The results, depicted in the Figure below, demonstrate that there is a significant decrease in the presynaptic terminal density in the Arg-61 mice compared to wt mice, indicating significant neurodegeneration in the one-year old Arg-61 mice.



5. This study provides a direct link of apoE domain interaction with neurodegeneration, which is a phenomenon associated with AD.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

2/22/05
Date

Karl H. Weisgraber
Karl H. Weisgraber

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